BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

Japanese Kokai Patent Application No. Hei 5[1993]-97681

Job No.: 473-82841
Translated from Japanese by the Ralph McElroy Translation Company
910 West Avenue, Austin, Texas 78701 USA

JAPANESE PATENT OFFICE
PATENT JOURNAL (A)
KOKAI PATENT APPLICATION NO. HEI 5[1993]-97681

Int. Cl.[5] :	A 61 K	31/765 9/20 9/28 31/765 47/38
Sequence Nos. for Office Use:	8314-4C 7329-4C	
Filing No.:	Hei 3[1991]-289211	
Filing Date:	October 8, 1991	
Publication Date:	April 20, 1993	
No. of Claims:	2 (Total of 5 pages)	
Examination Request:	Not filed	

AGENTS FOR REMOVING GAS IN THE DIGESTIVE TRACT

Inventor: Yukio Kawakami
6-8-617, 4-Chome, Senrigaoka higashi
Settsu-shi, Osaka-fu

Applicant: 591246997
Horii Yakuhin Kogyo K.K.
2-6, 1-Chome, Uchiawaji-machi, Chuo-ku
Osaka-shi, Osaka-fu

Agent: Michio Akaoka, patent attorney

Abstract

Objective

To provide formulations which can effectively exhibit the excellent antifoaming action of poly(dimethylsiloxane) at the regions where gas is accumulated in the digestive tract.

Constitution

They are poly(dimethylsiloxane)-containing formulations for oral administration composed of enteric solids coated with enteric films and solids not coated with enteric films; they are agents for removing gas in the digestive tract which are characterized in that 75-95% of the poly(dimethylsiloxane) is contained in the aforementioned enteric solids.

Claims

1. Agents for removing gas in the digestive tract, characterized in that they are poly(dimethylsiloxane)-containing formulations for oral administration composed of enteric solids coated with enteric films and solids not coated with enteric films, and 75-95% of the poly(dimethylsiloxane) is contained in the aforementioned enteric solids.

2. Agents for removing gas in the digestive tract described in Claim 1, characterized in that the form of the formulations includes two-layer tablets and core tablets or sugar-coated tablets.

Detailed explanation of the invention

[0001]

Industrial application field

The present invention pertains to formulations with poly(dimethylsiloxane) as the main ingredient, which is known as an agent for removing gas in the digestive tract. More precisely it pertains to formulations so designed that the efficacy of poly(dimethylsiloxane) can be enhanced.

[0002]

Prior art

There are many people who complain about various subjective abdominal symptoms without the consistent symptoms which accompany various digestive tract diseases, such as meteorism, abdominal distension, abdominal pain, belching, flatulence, feeling of oppression, borborygmus, heartburn, constipation, diarrhea, nausea, loss of appetite, etc. The cause of these symptoms is mainly the increase of gas in the digestive tract. It is said that there is usually approximately 1,000 mL of gas in a human body under normal physiological conditions. Of this, approximately 50 mL of gas is in the bottom part of the stomach to form the stomach gas

bubbles, there is almost no gas in the small intestine, and most of the remaining gas is in the large intestine. Approximately 70% of the gas is swallowed air and it enters the digestive tract with food, water and other beverages, especially carbonated beverages. And it is believed that approximately 20% of the gas diffuses into the intestinal tract from the blood, and the remainder is generated from decomposition and fermentation in the intestinal tract, especially in the ascending and transverse colon.

[0003]

The amount and the composition of the gas in the digestive tract depend greatly on the properties of the foods ingested and factors such as intestinal motility, however, causes of increased gas can include the following

(1) Aerophagy

Aerophagy can be found in many nervous people and they swallow air unconsciously, and in this case belching always occurs. Sometimes meteorism develops and disorders of the stomach and intestines are the complaint.

(2) Acceleration of formation of gas in intestinal tract

Much of the acceleration of formation of gas in the intestinal tract is caused by decomposition and fermentation in the intestinal tract. Especially when there is an increased motility of the large intestine or insufficient digestion and absorption of food, the greater part of the food residues are subjected to bacterial decomposition in the first half of the large intestine and produce gas. Generally speaking, after digestive tract surgery, the digestive absorption function is temporarily inadequate, and especially after surgical removal of the stomach the amount of hydrochloric acid secreted is reduced, so the bacteria in the lower intestinal tract move to the upper intestinal tract and bring about abnormal fermentation, therefore in many cases people complain of abdominal distension.

(3) Obstruction of absorption of gas in the intestinal tract

This can be observed in various circulatory disorders in the mesentery and the portal vein.

(4) Excretion disorder of gas in the intestines

When the passing of the contents in the intestines is mechanically hindered due to adhesion, bending, or stricture of the intestinal tract, the stagnant contents are decomposed by bacteria and the accumulation of gas is increased. Thereby the expansion of the intestinal tract is

increased, therefore a local circulatory disorder occurs and the obstruction of the absorption of gas is further increased.

[0004]

For the treatment of various subjective abdominal symptoms without consistent symptoms caused by the gas accumulated in the digestive tract, poly(dimethylsiloxane) is used widely both in Japan and other countries, and it is reported to be at least 70% effective. This is effective not only for treatment of various subjective abdominal symptoms without consistent symptoms, but also for removing gas inside the intestines which can hinder diagnosis by x-ray examination of the abdomen.

[0005]

Poly(dimethylsiloxane) cannot be absorbed from the digestive tract and it has the characteristics of low toxicity, being unaffected by enzymes, and does not inhibit bacterial activity, and its excellent antifoaming action in the stomach and intestines can be seen in many reports.

[0006]

By its surface active action, poly(dimethylsiloxane) lowers the surface tension of the gas bubbles in the digestive tract and bursts the gas bubbles to form a mass of free gas, thereby facilitating the absorption of the gas in the intestinal tract by the flow of blood and the discharge of the gas to outside the human body.

[0007]

The present commercially available formulations of poly(dimethylsiloxane) are tablets, powders, granulates, syrups, etc. Among these formulations, the syrup formulation is often used for removing viscous liquid inside the stomach containing gas bubbles at the time of endoscopic examination of the stomach rather than for improving the various subjective abdominal symptoms without consistent symptoms by removing the gas inside the intestinal tract. Thus many types of poly(dimethylsiloxane) formulations are commercially available, however, formulations which were designed for exhibition of effectiveness in all the regions where gas is accumulated, which is the cause of various subjective abdominal symptoms without consistent symptoms have not yet been known.

[0008]

Problem to be solved by the invention

The object of the present invention is to exhibit more effectively the excellent antifoaming action of poly(dimethylsiloxane). Namely to efficiently exhibit the action of poly(dimethylsiloxane), especially at the regions where gas is readily accumulated in the digestive tract.

[0009]

As already mentioned above, a portion of the gas in the digestive tract is at the bottom part of the stomach and a greater portion is in the large intestine. However, conventional formulations were not devised in such a way as to make poly(dimethylsiloxane) act most efficiently in the large intestine.

[0010]

Means to solve the problem

The present invention is solid formulations for oral administration composed of a part which is soluble in the gastric juice containing a suitable amount of poly(dimethylsiloxane) for removing a certain amount of gas at the bottom part of the stomach and an enteric part containing a suitable amount of poly(dimethylsiloxane) for removing the gas in the intestines.

[0011]

Namely the present invention is a formulation for oral administration which is characterized in that it is composed of an enteric solid part coated with an enteric film and containing poly(dimethylsiloxane) and a necessary excipient and a solid part not coated with an enteric film but containing poly(dimethylsiloxane) and a necessary excipient which covers all or part of the enteric solid part; and 75-95% of the poly(dimethylsiloxane) in the whole formulation is contained in the enteric solid part and the remainder is contained in the solid part not coated with the enteric film.

[0012]

The amount of the poly(dimethylsiloxane) in the formulation of the present invention can be adjusted depending on the size of the formulation, the amount of gas in each region of the digestive tract, etc. However, generally at least 20 mg, usually 30 mg, is in the enteric solid part and approximately 1/3 of that amount is contained in the solid part not coated with the enteric film. In case the amount of gas at the bottom part of the stomach is relatively small, for example, corresponding to the symptoms, 95% (e.g., 38 mg) of the total amount of poly(dimethylsiloxane)

(e.g., 40 mg) is contained in the enteric solid part and 5% (e.g., 2 mg) is contained in the solid part not coated with the film for suiting the symptoms.

[0013]

The enteric film can be coated using a common enteric coating material such as hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate, etc., and using a common method.

[0014]

The formulation of the present invention can also be made into two-layer tablets, core tablets, sugar-coated tablets, etc., using common methods.

[0015]

The present invention is constituted as above, therefore an optimum amount of poly(dimethylsiloxane) can be released at each region where gas in the digestive tract is readily accumulated and its antifoaming effect can be exhibited very efficiently.

[0016]

Application examples

In the following, in order to explain the present invention in more detail, experimental examples will be described for making clear the application examples of the formulations of the present invention and their effect. For all the application examples, the poly(dimethylsiloxane) contained in the outer part of the formulation is released in the acidic pH in the stomach and immediately exhibits antifoaming activity, and the poly(dimethylsiloxane) contained in the inner part of the formulation, namely the part coated with an enteric film, is released in the alkaline pH inside the intestines and exhibits antifoaming activity at that part.

[0017]

Application Example 1 (sugar-coated tablets)

30 mg of poly(dimethylsiloxane) was adsorbed by 40 mg of magnesium aluminate metasilicate and 30 mg of dextrin (Japanese Pharmacopoeia), then an excipient was added, and then it was made into a tablet to give a 250 mg principle tablet, which was then coated with a 20 mg of hydroxypropylcellulose phthalate film. Then in a sugar-coating pan, it [the coated tablet] was sprinkled with a dusting powder for subcoating with which 10 mg of poly(dimethylsiloxane) was previously mixed, then a gelatin solution was added. This operation

was repeated. Then a smoothing solution was added, then after dried thoroughly, a sugar syrup was added to gloss.

[0018]

Application Example 2 (Core tablet)

30 mg of poly(dimethylsiloxane) was adsorbed by 40 mg of magnesium aluminate metasilicate and 30 mg of dextrin (Japanese Pharmacopoeia), then an excipient was added, and then it was made into a tablet to give a 250 mg principle tablet, which was then coated with a 20 mg of hydroxypropyl cellulose phthalate film. The coated tablet was used as a center tablet which was then made into a tablet using a compression coating machine. The compression coating process was as follows:

1) Approximately half the amount (containing 5 mg of poly(dimethylsiloxane)) of the powder for the outer layer was poured into a mortar.

2) The above-mentioned center tablet as a core was put on its central part.

3) The remaining approximately half the amount (containing 5 mg of poly(dimethylsiloxane)) of the powder for the outer layer was poured onto it, then compression molding was carried out.

[0019]

Experimental examples

Whether or not the product (sugar-coated tablet) of the present invention prepared in Application Example 1 was able to disintegrate approximately equally in the stomach and intestines within a fixed period of time and exhibited efficacy in the stomach and intestines was examined using the disintegration test method prescribed by the Japanese Pharmacopoeia, and its efficacy was confirmed by an antifoaming test.

[0020]

Experimental Example 1 (disintegration test)

The product of the present invention was a formulation prepared for reliably exhibiting the effect both in the stomach and the intestines, therefore the test was carried out based on the Japanese Pharmacopoeia's "disintegration test" for enteric formulations.

(1) Test using the first solution

The first solution (pH 1.2) was used as the test solution, and an auxiliary pan was used, then a vertical (up-and-down) motion was carried out for 30 min, and the time required for the

outer layer to break down was measured (Table 1). At that time no abnormality, such as opening, peeling, or damage, of the film of the inner core tablet coated with an enteric film was observed.

Table 1. Test results using the first solution (disintegration time of the outer layer)

錠剤No.	崩壊に要する時間	錠剤No.	崩壊に要する時間
1	8分13秒	7	10分12秒
2	8分24秒	8	10分30秒
3	9分03秒	9	11分01秒
4	9分17秒	10	12分46秒
5	9分49秒	11	13分29秒
6	10分11秒	12	13分38秒

Key: 1 Tablet No.
2 Time required for disintegration
3 Minutes
4 Seconds

(2) Test using the second solution

After the test instrument was gently removed, the beaker containing the second solution (pH 6.8), whose temperature and quantity were adjusted, was immersed and an auxiliary pan was put in, and after the vertical motion was carried out for 60 min, it was observed that there was no residue of the sample in the glass tube. (Table 2).

Table 2. Test results using the second solution (disintegration time of the inner core tablet)

錠剤No.	崩壊に要する時間	錠剤No.	崩壊に要する時間
1	8分13秒	7	10分12秒
2	8分24秒	8	10分30秒
3	9分03秒	9	11分01秒
4	9分17秒	10	12分46秒
5	9分49秒	11	13分29秒
6	10分11秒	12	13分38秒

Key: 1 Tablet No.

2 Time required for disintegration
3 Minutes
4 Seconds

Experimental Example 2 (test for antifoaming power)

Approximately 100 mL of a test solution (the first and the second solutions in which 1% gelatin was dissolved in each solution) was put in a tall 200 mL beaker, then the solution was stirred at a fixed rate (4000 rpm) for 1 min using a homogenizer, and the height of the foam was measured after stirring. Subsequently the sugar-coated part was broken down using a small quantity of the first solution, then the disintegration solution was added to the foamed test solution (first solution containing 1% gelatin), then it was stirred for 1 min, then the height of the foam was measured. The amount added corresponded to the amount of poly(dimethylsiloxane) as per Table 3. The remaining enteric part was likewise disintegrated with a small quantity of the second solution, then the thus obtained disintegration solution was added to a foamed test solution (second solution containing 1% gelatin), it was stirred for 1 min, then the height of the foam was measured.

Table 3. Results of the test of antifoaming power

試験液の種類 ② / ジメチルポリシロキサン量 ①	1％1液ゼラチン液 ③	1％2液ゼラチン液 ④
0	30 mm	31 mm
1 mg	19 mm	28 mm
2 mg	7 mm	21 mm
3 mg	4 mm	17 mm
4 mg	2 mm	13 mm
5 mg	1 mm	11 mm
10 mg	0	6 mm
20 mg		1 mm
30 mg		0

Key: 1 Amount of poly(dimethylsiloxane)
2 Type of test solution
3 First solution containing 1% gelatin
4 Second solution containing 1% gelatin

As a result it was confirmed that when the amount of poly(dimethylsiloxane) added was 10 mg and 30 mg in the first and second solutions containing 1% gelatin, respectively, complete antifoaming effect was obtained. The above results also show the same antifoaming power when poly(dimethylsiloxane) was added to the test solutions under the same foaming conditions.